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Serotonin in Fear and Anxiety

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Hörsal Carl Kylberg (K2320), Medicinaregatan 7B, fredagen den 6 november, klockan 13:00

av Melker Hagsäter

Fakultetsopponent: Prof. Gregers Wegener,
Aarhus University, Denmark

Avhandlingen baseras på följande delarbeten

I. **Hagsäter SM**, Pettersson R, Holmäng A and Eriksson E, "Serotonin depletion reduces both acquisition and expression of context-conditioned fear", *Submitted*

II. **Hagsäter SM**, Pettersson R, Pettersson C, Atanasovski D, Näslund J and Eriksson E, "A complex impact of the 5-HT_{2A} receptor on conditioned fear revealed by systemic administration of different 5-HT_{2A} ligands including pimavanserin and psilocybin", *Submitted*

III. Pettersson R, **Hagsäter SM**, Carlsson B, Karlsson L and Eriksson E, "Chronic but not acute administration of escitalopram reduces context-conditioned fear", *Submitted*

IV. **Hagsäter SM**, Thorén J, Pettersson R and Eriksson E, "Selective serotonin reuptake inhibition increases noise burst-induced unconditioned and context-conditioned freezing", *Acta Neuropsychiatrica*, 2019, **31**, 46-51

V. **Hagsäter SM**, Lisinski A and Eriksson E, "5-HT_6 receptor antagonism reduces defecation in rat: A potential treatment strategy for irritable bowel syndrome with diarrhea", *European Journal of Pharmacology*, 2019, **864**, 172718

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR NEUROVETENSKAP OCH FYSIOLOGI

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Serotonin in Fear and Anxiety

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Abstract

That the neurotransmitter serotonin (5-HT) has a central role in fear and anxiety is supported by numerous experimental and clinical studies. Arguably the most illustrative example is the effect of serotonergic-acting drugs, and in particular the selective serotonin reuptake inhibitors (SSRIs), in the treatment of anxiety disorders. Interestingly, long-term administration is required to induce a dampening effect on anxiety, while on the contrary acute administration can aggravate the symptoms in susceptible individuals.

Freezing behaviour is a well-established measure of fear and anxiety, foremost assessed in studies performed on rodents. The bulk of the experiments presented in this thesis investigate the effect of pharmacological manipulations of the serotonin system on conditioned and unconditioned freezing behaviour.

In paper I, the importance of an intact serotonergic neurotransmission in fear conditioning was explored. The serotonin system was compromised by administration of the serotonin-depleting agent *para*-chlorophenylalanine (PCPA). PCPA impaired both acquisition and expression of conditioned fear without imposing an effect on memory consolidation, supporting the notion that fear-induced release of serotonin primarily promotes rather than dampens fear conditioning.

In paper II, the effects of 5-HT_{2A} receptor agonism and antagonism alone and in combination with administration of an SSRI were investigated. The first main finding was that while administration of neither the 5-HT_{2A} receptor antagonist MDL 100907 nor the 5-HT_{2A} receptor inverse agonist pimavanserin consistently reduced expression of conditioned freezing, a marked reduction of fear was observed after administration of either drug combined with an SSRI. The second main finding was that administration of both a selective agonist for the 5-HT_{2A} receptor and the psychedelic drug psilocybin reduced expression of conditioned freezing, an effect that was totally abolished by co-administration with MDL 100907. The experiments demonstrated that the 5-HT_{2A} receptors have the ability to modulate fear expression in both directions, putatively involving 5-HT_{2A} receptor populations in different areas of the brain.

In paper III, the effects of chronic and acute administration of an SSRI were compared. Chronic administration but not acute administration induced a dampening effect on anxiety. Since these findings mirror the clinical situation, context-conditioned freezing could supposedly be applied in animal studies on the mechanism of action for the sluggish effects of SSRIs in anxiety disorders.

In paper IV, the effect of acute administration of an SSRI was evaluated in a model of unconditioned fear. Acoustic noise bursts constituted the unconditioned stimulus. The SSRI increased the expression of unconditioned fear. Unconditioned models are tentatively related to panic disorder, the condition in which aggravation of anxiety after acute administration of an SSRI is most pronounced, suggesting that noise burst induced freezing presumably could be a useful tool in preclinical studies on the anxiety-provoking effects of SSRIs.

In paper V, the effect of 5-HT_6 receptor manipulations on gut motility was explored. It was found that 5-HT_6 receptor antagonists reduced defecation in both stressed (fear conditioned) and non-stressed animals while an agonist for the same receptor was void of effect. This mechanism could putatively be utilized in the treatment of irritable bowel syndrome with diarrhea (IBS-D).

In summary, the studies on rats presented in this thesis suggest that i) intact serotonergic transmission is required for both acquisition and expression of conditioned fear, ii) that the 5-HT_{2A} receptor has an important role in modulating conditioned fear, iii) that chronic administration of an SSRI, in contrast to acute administration, reduces conditioned fear, iv) that acute administration of an SSRI increases unconditioned fear and v) that 5-HT_6 receptor antagonism impairs gut motility.

Keywords: serotonin, fear, anxiety, SSRI, IBS

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